

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.

The Topical Use of Kappa Opioid Agonists to Treat Ocular Pain

5

The present invention relates to the pharmaceutical treatment of pain. In particular, the present invention relates to the topical use of kappa opioid receptor agonists and partial agonists for the prevention or alleviation of pain in the eye.

10 Background of the Invention

Pain is a perceived nociceptive response to local stimuli in the body. The perception of pain at the level of the central nervous system requires the transmission of painful stimuli by peripheral sensory nerve fibers. Upon stimulation of tissue (i.e., thermal, mechanical or
15 chemical), electro-chemical signals are transmitted from the sensory nerve endings to the spinal column, and hence to the brain where pain is perceived.

The cornea is highly innervated with sensory afferents which transmit various painful stimuli to the central nervous system. Pain conditions involving the eye, therefore, can arise in numerous instances, such as: foreign body stimulus, inflammation, dry eye syndrome, accidental trauma, surgical procedures and post-surgical recovery. For example, ocular pain
20 can result from photorefractive keratotomy ("PRK"), a vision correcting, surgical procedure whereby a laser is used to shape the cornea. This process involves the photoablation of Bowman's membrane and the stromal levels of the cornea. As a result, the denuding of the nerve-containing epithelial layers of the cornea can cause some patients to experience pain
25 following laser surgery until the epithelium regenerates.

Various therapies have been attempted for the alleviation of pain. The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, have been developed to treat pain. These agents inhibit cyclooxygenase dependent prostaglandin synthesis.

Prostaglandins can modulate pain perception at the level of the central nervous system and systemic administration of NSAIDs is known to provide analgesia. However, the use of NSAIDs can involve undesired side effects including gastrointestinal bleeding and kidney dysfunction.

5 Local anesthetics are another class of pain modulators which relieve pain by directly inhibiting nerve cellular function. One problem with local anesthetic therapy is that the anesthetics exhibit a short duration of action. Another problem with the use of local anesthetics is that their mechanism of action, non-specific membrane stabilization, can have the undesired coincident effect of also inhibiting biological functions of other cells, such as
10 fibroblasts and surrounding neural cells. Therefore, even though pain sensation can be abated with local anesthetic treatment, healing and normal function of the tissue may be significantly compromised. There is a need, therefore, to discover agents which potently and specifically inhibit the transmission of painful stimuli by sensory afferents, without local anesthetic activity, following topical ocular application.

15 Other agents have also been suggested for use in treating pain. Such agents include tricyclic antidepressants such as imipramine and desipramine, alpha-2 adrenergic agonists, serotonin uptake blockers, such as prozac, and other analgesics such as paracetamol, as described in United States Patent No. 5,270,050 (Coquelet et al.). Some of these therapies, however, have been associated with side-effects such as dryness of mouth, drowsiness,
20 constipation, and low potencies and efficacies.

Opiates are another class of compounds used to treat pain. Opiates can be administered in a number of ways. For example, opiates can be administered systematically, by intravenous injection or oral dosage, or locally, by subcutaneous, intramuscular or topical application. Systemic administration of opiates, however, has been associated with several

problems including dose escalation (tolerance), addiction, respiratory depression and constipation.

“Opioids” is a generic term of art used to describe molecules that produce morphine - like activity in the body. Opioid receptors are membrane proteins which generally cause analgesic responses when bound by opioids. There are three major categories of opioid receptors, designated μ (mu), κ (kappa) and δ (delta). Other sub-type receptors appear to exist as well. Opioid receptors have been differentiated among each other by the preferential binding affinities of different agonists and antagonists, and by the different responses obtained from each receptor’s binding. For example, the full agonist morphine has a ten times greater affinity for the mu receptor than for the delta and kappa receptors. Thus, morphine is a mu agonist (See, Goodman and Gilman’s Pharmacological Basis of Therapeutics (8th Edition), Jaffee, *Chapter 21: Opioid Analgesics And Antagonists*, page 485-492 (1993).) Kappa receptors have also been delineated from the general class of opioid receptors by the fact that mu and delta receptor agonists increase membrane potassium conductance and decrease the duration of presynaptic action potential, whereas kappa receptor agonists decrease voltage-dependent calcium conductance without affecting potassium conductance (Kanemasa, *k-opioid agonist U50488 inhibits P-type Ca^{2+} channels by two mechanisms*, Brain Research, volume 707, pages 207-212 (1995)).

While it is known that opiate analgesics such as morphine relieve pain by activating specific receptors in the brain, recent studies demonstrate the analgesic effects of compounds which act on kappa receptors in peripheral tissue. (See, Joris et al., *Opiates suppress carrageenan - induced edema and hypothermia at doses that inhibit hyperalgesia*, Pain, volume 43, pages 95-103 (1990); Eisenberg, *The peripheral antinociceptive effect of morphine in a rat model of facial pains*, Neuroscience, volume 72, No. 2, pages 519-575

(1996); and Gohschlich, *The peripherally acting k-opiate agonist EMD 61753 and analogues: opioid activity versus peripheral selectivity*, Drugs Exptl. Clin. Res., volume XX1(5), pages 171-174 (1995)).

5 Summary of the Invention

The present invention is directed to compositions and methods of treating ocular pain. The present invention is based in part on the finding that compounds which bind to kappa opioid receptors in the eye inhibit ocular pain. More specifically, the present invention
10 provides compositions containing kappa opioid agonists for the treatment of ocular pain.

The methods of the present invention involve the topical dosage of the compositions described below. One advantage of this therapy is that the inhibition of pain is receptor-specific, as contrasted with non-specific therapy, such as local anesthetic treatment. This specific activity may reduce greatly the number of dosings per day, and also reduce other
15 drawbacks such as short duration of action and inhibition of wound healing, which are associated with local anesthetics. Additionally, kappa opioid receptor binding agents acting locally within ocular tissue avoid the problems of tolerance, addiction and constipation associated with the chronic, systemic administration of opiates.

20 Detailed Description of the Invention

The present invention is directed to the use of kappa opioid receptor agonists for the prevention or alleviation of pain. It has now been found that kappa opioid agonists potently prevent or alleviate ocular pain. The kappa opioid receptor is found principally in the spinal

cord, but recent evidence of other peripherally located kappa receptors has been reported, as described above.

The compounds of the present invention are kappa opioid receptor agonists. As used herein, a "kappa opioid agonist" refers to a compound which activates a kappa opioid
5 receptor. Other opioid receptor agonists, such as mu and delta are excluded from the present invention compounds.

The kappa opioid receptor agonists of the present invention are known or may be elucidated by various biological binding studies known in the art. For example, the kappa opioid agonists of the present invention may be ascertained by displacement studies involving
10 the binding of known radioactive agonists, such as U69593, with target tissue slices or homogenates (Gohschlich, Drugs Exptl. Clin. Res., Volume XX1(5), pages 171-174 (1995)).

The following compounds are examples of kappa opioid agonists, listed as their trade name/number: enadoline, ICI-199441, R-84760, ZT-52656A, tifluadom, PD-117302, PD-129290, MR-1268, KT-90, GR-45809, GR-89696, GR-103545, GR-45809, GR-94839,
15 xorphanol, RU-49679, fedotozine, DuP-747, HN-11608, RP-60180 U-69593, U-62066 spiradoline mesylate, and trans-U-50488 methane sulfate. Preferred kappa opioid compounds of the present invention are those which only act in the periphery and do not cross the blood-brain barrier, or have limited CNS effects, such as EMD-60400 and EMD 61753. The most preferred kappa opioid agonist is EMD-61753. The kappa opioid agonists of the present
20 invention are available from commercial sources or may be synthesized by methods known to those skilled in the art.

The following is an example of the ocular anti-pain efficacy of representative kappa opioid receptor agonists of the present invention, as compared with other agents:

Example 1

Representative compounds of the present invention, a mu agonists (morphine) and a local anesthetic (Alcaine®, Alcon Laboratories, Inc, Fort Worth, TX) were tested in a formalin-induced model of ocular pain in the rat. Briefly, 20 μ L of the compound to be tested or vehicle (maxidex vehicle) were applied topically at various times between 1 and 30 minutes prior to the administration of formalin. 5 μ L of a 0.1% w/v formalin solution (5 μ g) was then topically applied using an eppendorf pipette. Blinking began immediately and the frequency over the first minute was determined. The 5 μ g dose of formalin typically yielded about 40-50 blinks in the first minute. The control counts of vehicle animals were compared to the counts of dosed animals and percent inhibition was then calculated. The results are illustrated in Table 1 below:

Table 1

Compound	Type	%w/v	% Inhibition
Alcaine	local anesthetic	0.5	94
GR 89696	kappa opioid agonist	0.1	98
U-69593	kappa opioid agonist	0.1	63
U-62066 spiradoline mesylate	kappa opioid agonist	0.1	68
trans-U-50488 methane sulfate	kappa opioid agonist	0.1	64
Morphine	mu opioid agonist	1.0	8

As can be seen from Table 1, the topical administration of kappa opioid agonists was effective in inhibiting ocular pain in the rat, in contrast to the topical administration of the mu agonist, morphine.

The kappa opioid agonists of the present invention will be contained in compositions, in accordance with formulation techniques known to those skilled in the art. The compounds may be included in solutions, suspensions and other dosage forms adapted for the particular kappa opioid agonist and dosing regimen.

5 The present invention is particularly directed to the provision of compositions adapted for topical treatment of ophthalmic tissues. The ophthalmic compositions of the present invention will include one or more kappa opioid agonists and a pharmaceutically acceptable vehicle for these agonist(s). Various types of vehicles may be used. The vehicles will generally be aqueous in nature. Aqueous solutions or suspensions are generally preferred, based on ease
10 of formulation, as well as a patient's ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compounds of the present invention may also be readily incorporated into other types of compositions, such as suspensions, viscous or semi-viscous gels or other types of solid or semi-solid compositions. Suspensions may be preferred for kappa opioid agonists which are relatively insoluble in water.
15 The ophthalmic compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

An appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

Ophthalmic products are typically packaged in multidose form. Preservatives are thus
20 required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0 percent by weight, based on the total weight of the composition (wt.%).

Some of the compounds of the present invention may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: polyethoxylated castor oils, Polysorbate 20, 60 and 80; Pluronic® F-68, F-84 and P-103 (BASF Corp., Parsippany NJ, USA); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01 to 2 wt.%. 5

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01 to 2 wt.%. 10

The compounds may also be used for treating irritated tissues following ophthalmic surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive ophthalmic procedures, or other types of surgery. 15

The compounds and compositions of the present invention will be used to prevent or ameliorate ocular pain associated with various stimuli. For example, the kappa opioid agonists and compositions of the present invention may be used in treating pain arising from allergens, inflammation, trauma, dry eye, foreign body sensation, such as from contact lenses and surgery. 20 The compounds of the present invention may be used for the treatment of pain following ocular surgery, such as PRK surgery. With such treatment, the kappa opioid agonists can be individually dosed, or in combination with other pharmaceutical agents such as by methods

disclosed in U.S. Patent Nos. 4,939,135 and 5,401,510 (Robertson et al.), the entire contents of which are incorporated herein by reference. The compounds will be utilized in a concentration effective to prevent or ameliorate ocular pain. As used herein, the term "pharmaceutically effective amount" refers to that amount of one or more kappa opioid agonists which prevents or alleviates ocular pain. In general, the dosage of kappa opioid agonists utilized for any of the above-described purposes will generally be from about one to two drops of a 0.01 wt.% to 3 wt.% composition, administered one to four times per day.

The compositions of the present invention are further illustrated by the following formulation Examples 2-4. The ingredient "kappa opioid agonist" denotes a compound of the present invention.

Example 2

Ingredient	Amount (wt%)
EMD-61753	0.01-1.0%
Phosphate Buffered Saline	1.0
Polysorbate 80	0.5
Purified water	q.s. to 100%

Example 3

5	Ingredient	Amount (wt%)
	kappa opioid agonist	0.01-1.0%
	Monobasic sodium phosphate	0.05
	Dibasic sodium phosphate	0.15
10	(anhydrous)	
	Sodium chloride	0.75
	Disodium EDTA (Edetate disodium)	0.05
	Cremophor EL	0.1
	Benzalkonium chloride	0.01
15	HCl and/or NaOH	pH 7.3 - 7.4
	Purified water	q.s. to 100%

20

Example 4

25	Ingredient	Amount (wt%)
	kappa opioid agonist	0.01-1.0%
	Phosphate Buffered Saline	1.0
	Hydroxypropyl- β -cyclodextrin	4.0
30	Purified water	q.s. to 100%

What is claimed is:

1. A composition for topically treating ocular pain comprising a pharmaceutically effective amount of one or more kappa opioid agonist(s) in a
5 pharmaceutically acceptable vehicle.

2. A composition according to Claim 1, wherein the kappa opioid agonist is selected from the group consisting of: EMD-60400, EMD-61753, enadoline, ICI-199441, R-84760, ZT-52656A, tifluadom, PD-117302, PD-129290, MR-1268, KT-90, GR-45809, GR-
10 89696, GR-103545, GR-45809, GR-94839, xorphanol, RU-49679, fedotozine, DuP-747, HN-11608, RP-60180 U-69593, U-62066 spiradoline mesylate, and trans-U-50488 methane sulfate.

3. A composition according to Claim 2, wherein the kappa opioid agonist is
15 EMD-61753.

4. A method for treating ocular pain which comprises administering to a human a composition comprising a pharmaceutically effective amount of one or more kappa opioid agonist(s) in a pharmaceutically acceptable vehicle.

20

5. A method according to Claim 4, wherein the kappa opioid agonist is selected from the group consisting of: EMD-60400, EMD-61753, enadoline, ICI-199441, R-84760, ZT-52656A, tifluadom, PD-117302, PD-129290, MR-1268, KT-90, GR-45809, GR-89696, GR-103545, GR-45809, GR-94839, xorphanol, RU-49679, fedotozine, DuP-747, HN-11608,
25 RP-60180 U-69593, U-62066 spiradoline mesylate, and trans-U-50488 methane sulfate.

6. A method according to Claim 5, wherein the kappa opioid agonist is EMD-61753.

30

7. A method according to Claim 5, further comprising administering the composition topically.

8. A method according to Claim 6, further comprising administering the
5 composition topically.

9. A method according to Claim 5, wherein the ocular pain is the result of PRK surgery.

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/00, 31/135, 31/40, 31/55, 31/485, 31/54, 31/435, 31/495	A3	(11) International Publication Number: WO 98/26770 (43) International Publication Date: 25 June 1998 (25.06.98)
(21) International Application Number: PCT/US97/23185 (22) International Filing Date: 11 December 1997 (11.12.97) (30) Priority Data: 60/032,909 16 December 1996 (16.12.96) US (71) Applicant (for all designated States except US): ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): GAMACHE, Daniel, A. [US/US]; 5610 Hunterwood Lane, Arlington, TX 76017 (US). (74) Agents: MAYO, Michael, C. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 3 September 1998 (03.09.98)
(54) Title: THE TOPICAL USE OF KAPPA OPIOID AGONISTS TO TREAT OCULAR PAIN (57) Abstract Compositions and methods for treating ocular pain are disclosed. In particular, the invention discloses compositions and methods of using kappa opioid agonists topically for the prevention or alleviation of ocular pain.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/23185

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/00 A61K31/135 A61K31/40 A61K31/55 A61K31/485
A61K31/54 A61K31/435 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	UEDA ET AL.: "Dual effects of dynorphin-(1-13) on cholinergic and substance P-ergic transmissions in the rabbit iris sphincter muscle" J. PHARMACOL. EXP. THER., vol. 232, no. 2, 1985, pages 545-550, XP002068159 see the whole document	4
X	BARBER A ET AL: "A PHARMACOLOGICAL PROFILE OF THE NOVEL, PERIPHERALLY-SELECTIVE K-OPIOID RECEPTOR AGONIST, EMD 61753" BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, vol. 113, no. 4, 1994, pages 1317-1327, XP000611241 see the whole document	1-3
A	---	4-6
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

16 June 1998

Date of mailing of the international search report

0 2. 07. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gac, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/23185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GOTTSCHLICH R ET AL: "THE PERIPHERALLY ACTING K-OPIATE AGONIST EMD 61753 AND ANALOGUES: OPIOID ACTIVITY VERSUS PERIPHERAL SELECTIVITY" DRUGS UNDER EXPERIMENTAL AND CLINICAL RESEARCH, vol. 21, no. 5, 1995, pages 171-174, XP000609171 cited in the application see the whole document	1-3
A	---	4-6
X	WO 94 13275 A (MASSACHUSETTS EYE AND EAR INFIRMARY) 23 June 1994 see page 14 boxes 3 and 4 of Table 2 see page 11	1,2
X	--- EP 0 346 238 A (RHONE-POULENC SANTE) 13 December 1989 see page 2, line 25 - line 38 see page 38 lines 21, 44-48	1
A	--- EP 0 657 443 A (SANKYO COMPANY LIMITED) 14 June 1995 see lines 8-9, 20-24 -----	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/23185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 4-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/23185

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413275 A	23-06-1994	AU 683634 B	20-11-1997
		AU 5741494 A	04-07-1994
		CA 2150933 A	23-06-1994
		EP 0671910 A	20-09-1995
		JP 8506807 T	23-07-1996

EP 346238 A	13-12-1989	FR 2632520 A	15-12-1989
		AU 621120 B	05-03-1992
		AU 3624089 A	21-12-1989
		CA 1325631 A	28-12-1993
		DE 68906965 T	09-12-1993
		DK 283089 A	11-12-1989
		ES 2058569 T	01-11-1994
		IE 63300 B	05-04-1995
		IL 90559 A	26-08-1994
		JP 2504830 B	05-06-1996
		JP 3007269 A	14-01-1991
		MX 9203585 A	01-09-1992
		PT 90813 A,B	29-12-1989
		US 5049669 A	17-09-1991

EP 657443 A	14-06-1995	AU 4981693 A	29-03-1994
		FI 950878 A	29-03-1995
		NO 950731 A	21-04-1995
		US 5679674 A	21-10-1997
		AU 4001797 A	15-01-1998
		CA 2143449 A	17-03-1994
		CZ 9500525 A	18-10-1995
		HU 72636 A	28-05-1996
		WO 9405646 A	17-03-1994
		JP 6122677 A	06-05-1994
		NZ 255572 A	28-10-1996
